Metabolic Basis for Recommending How to Use Alcohol

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The rational use of alcohol by healthy persons aims to achieve some degree of intoxication—the drug effect of alcohol. A pattern of drinking that does this while minimizing the undesired toxic effects of alcohol may be inferred from an analysis of the metabolism of alcohol and the mechanisms of its toxic effects. While the intoxicant effect of alcohol depends on the quantity in the circulatory blood level, the toxic effects, particularly in the liver, depend largely on the total dose and are independent of the speed of absorption into the blood. Standards may be developed for the use of alcoholic beverages by healthy persons, based on these considerations. For the average person, a dosage of alcohol providing 175 calories and taken before a meal is unlikely to have significant toxic effects.

HOW CAN WE USE alcohol safely? What drinking patterns can we recommend to our community and to our patients?

To answer these questions fully requires a broad understanding of the biologic, pharmacologic, social, cultural, legal, and political factors involved in the use of alcohol. I focus here on the first of these factors, the biologic, as a means to begin developing this understanding. Analysis of the biologic effects of alcohol and processes of alcohol oxidation shows us how we may moderate or avoid the undesired effects on the body.

Alcohol affects the human body in two ways that differ fundamentally.[1] First, alcohol is a drug, with a pharmacologic effect reflected in intoxication. Second, alcohol is a food, with metabolic effects associated with its oxidation and the production of calories. The intoxicant effects of alcohol occur when alcohol enters the fluids bathing the central nervous system.[2] Intoxication level depends on the concentration of alcohol in the body fluids and this, in turn, depends on the amount consumed, the rapidity of absorption from the stomach and small intestine, and the body size of the drinker. In contrast, the metabolic effects occur as alcohol is oxidized, independent of the concentration in the body, and are more dependent on total dosage than on variations in intake and absorption patterns.

Uses of Alcohol

Alcohol finds its widest use as a drug taken to gain the intoxicant effects. Possibly the most used of all drugs, alcohol is consumed by about 60 to 70 percent of the adult population as a

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means of altering the function of the central nervous system in a way considered desirable in a variety of situations. Other quantitatively minor uses include those related to ceremonial and religious practices, cooking, and a number of social behaviors not independent of the drug function, such as business promotion or the celebration of marriages.[3] In the aggregate, the uses of alcohol for purposes unrelated to the drug function remain modest in relation to the total alcohol consumption in the community and, aside from the nonpharmacologic functions of drinking, the only rational reason for alcohol consumption is to obtain the drug effect—that is, some degree of intoxication.

The food value of alcohol may be considered as incidental to the drug effects. The food value lies in the caloric content—about seven calories per gram. Some alcoholic beverages, particularly beer and wines, also contain carbohydrates, and this adds significant nonalcoholic calories for these beverages (Table 1). In calculating the caloric value of alcoholic beverages, keep in mind the low density of alcohol—about 80 percent of that of water.* Thus, a gram of alcohol, providing seven calories, amounts to about 1.25 ml. One milliliter, therefore, provides 5.6 calories. This latter value should be used for calculating caloric value of beverages for which alcohol content is given in volume units or percentage concentration.[4]

Although the food value of alcohol is secondary to the drug value for the drinker, it contributes significantly to his total caloric intake. The average per capita alcohol consumption for the population of the United States is about 1.5 gallons per year. Assuming that all alcohol is consumed by that part of the population that makes up the drinking population, the average energy contribution of alcohol for drinkers is 175 to 200 calories daily. This probably is a low estimate.

Harmful Effects

Alcohol in excessive amounts damages the drinker through the social disruptions it produces, through accidents, particularly accidents due to drunk driving, and through toxic effects on the brain, the liver and other organs. My focus on the biologic factors in alcohol usage limits my consideration to the toxic effects on the body. The mechanism of the harmful effects on the brain are poorly understood, but appear at this time to be a direct effect proportionate to the concentration of alcohol in the body fluids and the duration of exposure.[2,5] In contrast, the effects on the liver result from metabolism of alcohol and are independent of concentration. Also, the mechanisms responsible here are extensively analyzed, and fairly complete explanatory models have been proposed.[6] Most of the evidence now emerging from the research laboratories supports the popular view of sufferers of the hangover, that alcohol is not without serious side effects.

Metabolism of Alcohol

Absorption occurs rapidly from the stomach and small intestine, the rate varying with the concentration of alcohol in the beverage and the presence or absence of other foods in the stomach. The most rapid absorption occurs when the stomach is empty. A single dose of alcohol on an empty stomach produces a considerably higher blood concentration than the same dose following food or divided and spaced out over a period of time. After absorption, rapid diffusion throughout the body fluids delivers alcohol to the brain and, also, to the liver, where it is oxidized. Minor amounts are oxidized in the kidneys and other sites, and a little escapes oxidation to be excreted in the breath or urine.

The rate of oxidation varies between individuals, ranging from about 60 to as much as 200 milligrams per kilogram of body weight per hour.[7] An average value may be taken to be 100 milligrams per kilogram per hour. In the Reference Man of 70 kilograms body weight, this would amount to about 1200 calories per day at the maximal rates possible. In short-term experiments, the ability to handle alcohol may range up to 2000 or 2400 calories for a person of this size. The oxidation rate is constant for an individual and independent of the concentration in body fluids, save at extremely low levels, since the mechanism for oxidation is saturated at all concentrations ordinarily encountered.

Oxidation proceeds in two steps, the first—the

*Alcohol combustion produces 7.0929 calories per gram. Precise expression of this in calories per milliliter requires specification of temperature. At 15.56° C. (standard), alcohol weighs 0.7930 grams per milliliter; at 20°, 0.7895; and at 25°, 0.7852. Therefore, to illustrate calculation, at 20° C. one ml of alcohol provides 0.7895 times 7.0929 or 5.5998 calories. The nutritive value of alcohol in a beverage is slightly less than the caloric value of the alcohol contained, since a small percent of the ingested alcohol is lost in the breath or urine.

rate-limiting step—yielding acetaldehyde, and the second step yielding acetate. The rate limitation in the first step depends on the availability of the necessary enzyme, alcohol dehydrogenase; and the variation in oxidative capacity between individuals is explained by individual variation in the activity of this enzyme in the liver. The acetate produced from oxidation of acetaldehyde may be further oxidized to carbon dioxide, or may enter a variety of metabolic processes, including the formation of fat or carbohydrate.

The significant event during the conversion of alcohol to acetate is a large production of hydrogen, amounting to four atoms per mole of alcohol.* This hydrogen is produced in the soluble cytoplasmic compartment of the cell during alcohol oxidation and loads up the cellular systems accepting it. It appears to be the key factor leading to profound alteration of diverse biochemical functions. Among the functions most prominently affected are fat and carbohydrate metabolism.**

The first system available within the cell to accept hydrogen produced during oxidation of alcohol is nicotinamide adenine dinucleotide (NAD). The massive loading of this acceptor is reflected in a threefold increase in the reduced form ($NADH_2$) during alcohol metabolism. This increase of $NADH_2$, in turn, is considered the first in a series of metabolic derangements of far-reaching effect. [6,8,9]

The most impressive metabolic effect of alcohol is the accumulation of fat in the liver, producing the characteristic swollen fatty liver of the heavy drinker. According to the concepts presented by Lieber,[6] the rise of $NADH_2$ during alcohol oxidation leads to fat accumulation through several paths. For example, one is through excess production of alpha-glycerophosphate as a result of reduction of dihydroxyacetone phosphate produced by glycolysis. Alpha-glycerophosphate, in turn, contributes to accumulation of triglyceride as a result of increased availability of the glycerol moiety of triglyceride and through stimulation of fatty acid synthesis. Another path proposed involves augmented fatty acid synthesis from acetylcoenzyme-A, resulting from impairment of alternative utilization of acetyl coenzyme-A in the citric acid cycle occurring during alcohol oxidation.

Another illustration of the diverse metabolic effects of the hydrogen donor property of alcohol is the loading of another hydrogen acceptor, pyruvate. This results in excess production of lactate and reduced availability of pyruvate for entry into the citric acid cycle. This shift of the pyruvate-lactate balance, in turn, plays a key role in impairment of gluconeogenesis and in producing the clinical syndrome of alcohol hypoglycemia.[10,11] Excess lactate production also raises the lactate level in the blood, which then causes a diminution of the ability of the kidney to excrete uric acid. This explains how alcohol may precipitate attacks of gout in susceptible persons.

Alteration of metabolic processes by alcohol in the heart, kidneys and other tissues appears to be responsible for some of the clinical syndromes affecting the heavy drinker, such as cardiac myopathy and alcoholic nephropathy.[9,12,13,14,15] In both the heart and the kidneys, the proportion of NAD in the reduced form increases with alcohol administration, indicating one important similarity to the biochemical effects of alcohol in the liver. However, the possible ways alcohol alters metabolism in these organs remain for the future to tell.

Alcohol and Cirrhosis

Associated with the biochemical disturbances caused by alcohol in the liver, extensive anatomic changes develop in the ultramicroscopic structures of the liver cells.[6] Most conspicuously, mitochondria enlarge and deform and their internal structure changes. Significant ultrastructural changes occur also in other cellular components. How these early anatomic lesions relate to the development of cirrhosis is yet unexplained. Although controversy about the pathogenesis of cirrhosis persists, accumulating evidence weighs in favor of the view that alcohol is an essential causative element. The most convincing support for this view comes from epidemiologic data that show striking correlations between the consumption of alcohol by a population or group and the occurrence of cirrhosis of the liver.[16] Although nutritional defects may accelerate the development of alcoholic

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*$CH_3CH_2OH \xrightarrow{-2H^+} CH_3CHO \xrightarrow[+H_2O]{-2H^+} CH_3COOH$

**The biochemical and anatomic disturbances produced in short-term experiments and reviewed here appear to be fully reversible following alcohol withdrawal. This accords with clinical observation that an arrest of progression occurs in patients with alcoholic diseases on cessation of drinking.

TABLE 1.—*Composition of Common Alcoholic Beverages*

Beverage	*Composition of 100 grams of Beverage*								*Volume Containing 175 Calories From Alcohol*
	Volume	*Alcohol*		*Water*	*Carbohydrate*	*Protein*	*Food Energy*		
	milli-liters[a]	*milli-liters*[a]	*grams*	*grams*	*grams*	*grams*	*from alcohol calories*[b]	*total calories*	*milli-liters*
Beer[c]	96.6	4.5	3.6	92.1	3.8	0.3	25	42	676
Distilled spirits[d]									
80-proof	109.0	42.3	33.4	66.6	trace	—	231	231	83
86-proof	109.9	45.6	36.0	64.0	trace	—	249	249	77
90-proof	110.2	48.0	37.9	62.1	trace	—	263	263	73
94-proof	110.7	50.3	39.7	60.3	trace	—	275	275	70
100-proof	111.4	53.8	42.5	57.5	trace	—	295	295	66
Dessert wines[e]	96.2	19.4	15.3	76.7	7.7	0.1	106	137	159
Table wines[f]	98.2	12.5	9.9	85.6	4.2	0.1	69	86	249

[a]Volume at 20 degrees Centigrade is calculated as $\frac{1}{0.99823}$ X grams of water plus milliliters of alcohol. Volume of alcohol is calculated as 1.267 times grams of alcohol, based on the density of alcohol at 20 degrees.

[b]A factor of 6.93 used to calculate calories from a gram of alcohol.

[c]The composition of beer varies widely, and these are average values. See: Davidson, C.S. "Nutrient Content of Beers and Ales," *New England Journal of Medicine,* 264:4 (January 26, 1961) 185-186.

[d]Distilled spirits include gin, rum, vodka, and whiskeys.

[e]Wines with over 15 percent alcohol by volume include ports, sherries, muscatel, tokay, and others. Content of alcohol and carbohydrate vary and values given are averages.

[f]Wines with under 15 percent alcohol by volume include many varieties of "dry" wines. Content of alcohol and carbohydrate vary and values given are averages.

Source: Modified from United States Department of Agriculture, Agricultural Research Service. *Composition of Foods,* Agriculture Handbook No. 8, 1963.

liver disease, these alone are not a sufficient cause for the production of portal cirrhosis in man.

Protection by Diet or Drugs

Since to many our culture dictates the use of alcoholic beverages, we seek ways other than abstinence to prevent the damaging effects of drinking. Folklore abounds with prescriptions for prevention or cure of hangovers and other complications of drinking, and the scientific community, too, has enthusiastically participated in the search for a means of protection. I regret that this effort has been largely fruitless. Studies of the factors affecting the accumulation of fat in the liver during alcohol oxidation illustrate this failure. Although modifications in the extent of fatty liver may occur, it cannot be prevented by massive doses of various vitamins or other additives, or by dietary manipulations such as elevation of the protein content to twice the recommended level.[6,17] Our inability to protect the liver by these means undoubtedly relates to the obligatory nature of the metabolic changes occurring in the liver during oxidation of alcohol. The rate of metabolism of alcohol and the associated loading of the cell with products of oxidation continue unaltered, despite manipulation of biochemical processes by drugs or diet modification.

How to Use Alcohol

This summary of the biologic effects and the metabolism of alcohol provides a basis for a recommendation about drinking patterns that serves to minimize the undesired effects on the body. The following statements apply to the normal person and in no way are applicable to the victim of alcoholism. I assume that an individual's total alcohol usage is modest or moderate, and I use as a standard for consumption my lower estimate for alcohol used by drinkers in the United States—the equivalent of 175 calories per day as alcohol, on the average.* This amount of alcohol, for example, is contained in 83 milliliters (less than two jiggers) of 80-proof liquor or in 159 milliliters (5.4 ounces) of dessert wine (Table 1). This standard for average consumption may be considered to be relatively liberal, since drinking may not be done every day

*I know of no evidence that tolerance of any significance for dosage develops at this level of alcohol consumption.

and the equivalent amount of alcohol accumulated over a number of days makes a rather large dose. Therefore, persons drinking intermittently should use a lower average amount.

The concept that the drug effects and metabolic effects of alcohol are relatively separate, and the idea that the drinker should minimize the metabolic effects associated with any given level of drug effect to be attained make the basis for a recommendation about drinking patterns. The drinker should seek the minimal dose of alcohol necessary to achieve the desired concentration of alcohol in the blood. To do this, he should drink under conditions that make for maximal blood concentration for a given dose. This means that alcohol should be consumed relatively rapidly and before meals.

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